UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/848,820	05/19/2004	Timothy A. McKinsey	MYOG:044US/10405748	4787

32425 7590 03/29/2010

FULBRIGHT & JAWORSKI L.L.P.
600 CONGRESS AVE.
SUITE 2400
AUSTIN, TX 78701

EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
03/29/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/848,820	MCKINSEY ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is responsive to papers filed 01/06/2010. Claim 1 has been amended. Claims 9-11 and 100 have been newly canceled and no claims have been newly added.

Currently claims 1-4, and 7-8 are pending.

Response to Amendment

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 7-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Dempsey (US 6,228,843) in light of Wang (Trends Pharmacol Sci, June 2006) and Matthews et al (J Biol Chem, August 1997) and in view of Metra et al (Heart Failure Reviews 1999).

Amended claim 1 is drawn to a method of inhibiting pathologic cardiac hypertrophy and hypertension in a human patient comprising: (a) identifying a human patient having cardiac hypertrophy and hypertension; (b) administering an inhibitor of PKD; and (c) administering a beta blocker, wherein the PKD inhibitor reduces hypertrophic signaling and inhibits hypertrophy in cardiac tissue of the patient and the beta blocker reduces hypertension in the patient.

Dependent claims include wherein the inhibitor of PKD is selected from a group, the type of administration and the timing of the beta blocker administration.

Dempsey teaches a treatment method of treating pulmonary and systemic diseases associated with cardiac hypertrophy and specifically includes hypertension associated with cardiac hypertrophy as one of the diseases treated (column 14 lines 28-38). Treatment can comprise administering several drugs to inactivate protein kinase C. Specifically the drugs taught include bryostatin and Go6976 (see Fig. 4; see col. 3 line 62 to line 67, as examples). Dempsey teaches that his method functions by first activating PKC which then causes its degradation (see col. 11 lines 35-40, for example).

Wang teaches that PKD is phosphorylated by PKC.

Matthews et al teach that bryostatin activates PKD through PKC (see Abstract, for example); therefore it is inherent that administration of bryostatin causes degradation of PKC and inhibition of PKD signaling and inhibits hypertrophy in cardiac tissue as taught by Dempsey.

These drugs in Dempsey are effective in primates including humans, reading on the limitation that the patient is human (see col. 4, lines 1-6, for example). The drugs administered in some combination with bryostatin include staurosporine, ACE-I (ACE inhibitors), and calcium channel blockers (Ca^{2+}-blocker) for example (see col. 12, lines 32-45, for example). They teach that the drugs can be administered in an oral or intravenous manner (see col. 6 lines 39-53, for example). Preferably the patient is treated by this method to an extent that the patient no longer suffers from the condition or wherein the discomfort and/or altered functions and detrimental conditions associated with the disease are decreased (column 9 lines 1-16).

The Wang and Matthews references are cited to provide evidence of the inherent property of bryostatin to act as a PKD inhibitor by causing the degradation of PKC and thus inhibiting PKD signaling.

Dempsey does not specifically teach administering the drug in combination with a beta blocker.

Metra et al teach that beta blockers when administered in combination with other drugs, such as ACE inhibitors, to patients with heart failure have been shown to be effective tools to improve cardiac function and the clinical course of the disease (page 65 column 1). Metra et al teach that the role of agents with proven efficacy on the survival and clinical course of the disease, like ACE inhibitors and beta blockers, as first line therapies for heart failure should be reinforced (page 68 column 2).

Therefore one of ordinary skill in the art would have been motivated to add the beta blockers and ACE inhibitors to the drug composition of Dempsey because Metra et al teach that these drugs have been shown to improve cardiac function and the clinical course of the disease and Dempsey suggests including drugs like ACE inhibitors as well. One of ordinary skill in the art would have had a reasonable expectation of success because Dempsey also suggests combining drugs known to be beneficial in the treatment of heart disease.

Therefore the combined teachings of Dempsey, Wang, Matthews et al and Metra et al render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments filed 01/06/2010 have been fully considered but they are not persuasive.

Applicant argues that discussing the references chronologically best illustrates what the prior art landscape was at the time of filing. Applicant asserts that the first paper in the chain of cited art was Matthews et al and that this reference describes bryostatin as an activator of protein kinase C (PKC) and protein kinase D (PKD).

The Matthews reference was cited in the obviousness rejection to demonstrate the inherent ability of bryostatin to act as a PKD inhibitor by causing the degradation of PKC and thus inhibiting PKD signaling. This reference provides the evidence for the manner in which bryostatin and staurosporine function in the method of Dempsey.

Applicant argues that the Dempsey reference is in stark contrast to Matthews as it describes bryostatin as an inhibitor of PKC, but only under certain conditions. Applicant argues that Dempsey teaches that bryostatin and other PKC activators are only PKC inhibtors when administered under higher concentrations. Applicant asserts that Dempsey does not teach anything about the ability to reverse activation of PKC and hence PKD by bryostatin.

This is not found persuasive as it is not necessary for the Dempsey reference to describe every advantage possible with the administration of bryostatin or other PKC inhibitors. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*,

227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Dempsey clearly teaches that there are substantial benefits of administering PKC inhibitors to a patient with cardiac hypertrophy and hypertension. The concentration of the drug is not a claim limitation and does not negate the teaching of Dempsey.

Applicant argues that Dempsey's results do not support Dempsey's conclusions. Applicant asserts that Dempsey does not provide sufficient evidence of efficacy. Applicant reviews table 1 and takes the error bars at their least favorable and suggests that the treatment might have resulted in absolute values that are roughly the average difference in untreated animals. Applicant points out that no *in vivo* data with either of the "true" PKC-inhibitors were provided.

This is not found persuasive because Dempsey clearly discloses that attenuating effects of bryostatin on the treatment of hypertension are produced (column 13 lines 40-47). In addition, it has been argued by Applicant (pages 2-3 of Applicant's remarks filed 09/07/2007) and agreed to by the Office (office action filed 11/29/2007, pages 2-3) that *in vivo* data are not required for the establishment of enablement especially with regard to the therapeutic use of a well established class of drugs such as PKC inhibitors.

Applicant argues that Wang is not prior art against the present claims and should not be considered when formulating an obviousness rejection.

This is not found persuasive because both the Wang reference and the Matthews references are cited in the rejection to demonstrate inherent facts with regard to the manner in which PKC inhibitors like bryostatin work. In certain circumstances, references cited to show a universal fact need not be available as prior art before

applicant's filing date. Such facts include the characteristics and properties of a material or a scientific truism. See M.P.E.P. § 2124 for relevant citations.

Applicants argue that the obviousness rejection is improper because it makes a number of assumptions regarding what those of skill in the art would have believed based on the cited art at the time of filing. Applicant asserts that no matter how bryostatin might be characterized in Dempsey, it is not a PKC or PKD inhibitor. Applicant refers to a wikipedia document concerning bryostatin as evidence. Applicant asserts that the fact that it might have inherently inhibited PKD at higher concentrations is not a fact that the skilled artisan could consider when assessing obviousness of its use in the claimed invention.

This is not found persuasive because Applicant has admitted that at higher concentrations the prior art does show bryostatin to demonstrate PKC inhibition (page 5 of Applicant's arguments filed 01/16/2010). In addition the Mathews reference and the Wang reference were cited by the Examiner to demonstrate the manner in which bryostatin functions to achieve the property of PKD inhibition as required by Applicant's claimed invention and carried out in the method of Dempsey. The claimed invention does not require a certain concentration of PKD inhibitor to be used only that one is used. Dempsey clearly teaches the use of PKC inhibitors and therefore PKD inhibitors for the treatment of cardiac hypertrophy and hypertension and therefore these limitations of the claimed invention are deemed to be met.

In addition, the Examiner requests that in the future Applicant provide a 1449 form when citing a reference that they wish the Office to consider. The Examiner has placed the wikipedia article on an 892 form to facilitate proceedings at this point.

Applicant argues that the evidence provided in Dempsey regarding Go6976 and GF1092203X is flawed. Applicant asserts that the concentrations used were non-physiologic and would hardly convince the skilled artisan to use these compounds to inhibit cardiac hypertrophy, even if they might be useful in inhibiting hypertension. Applicant argues that there would be no reason to equate data from bryostatin with Go6976 and GF1092203X for the simple reason that the latter two do not activate PKC at any concentration.

This is not found persuasive because Dempsey clearly teaches that these drugs are beneficial in the treatment of cardiac conditions related to hypertension. A patent is not required to exemplify every possible embodiment in order to be enabled. The artisan of ordinary skill in the art would have been motivated with a reasonable expectation of success to optimize the concentrations of the drugs by routine experimentation as the physical condition of the patient would have been a result effective variable.

Applicant argues that there is no evidence to suggest that bryostatin had any actual effect on hypertrophic signaling in Dempsey's studies. Applicant asserts that there is nothing in Dempsey's work to suggest that "true" PKC inhibitors would be useful in treating cardiac hypertrophy.

This is not found persuasive because inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not

recognize the inherent characteristics or functioning of the prior art. However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition or method patentably new to the discoverer. The cited references demonstrate that bryostatin has the inherent ability to acts as a PKC inhibitor at the disclosed concentrations and therefore the properties of administering a PKD inhibitor as claimed are deemed to be met. However, even if Applicant were correct and bryostatin did not qualify as a PKC/PKD inhibitor, Dempsey clearly teach the benefit of administering other PKC inhibitors such as staurosporine to a patient with the cardiac disorders of hypertrophy and hypertension.

Applicant argues that because the claims now include the limitations of treating hypertrophy itself and not just the symptoms of hypertrophy, that the cited prior art references are not sufficient to meet this new limitation in the amended claims. Applicant asserts that this feature is lacking in the prior art and thus the skilled artisan, when presented with the goal of treating hypertrophy, would not have turned to either bryostatin or a true PKC inhibitor.

This is not found persuasive because Dempsey teaches a method for treating cardiac hypertrophy with PKC inhibitors (see claim 1, column 14 lines 26-33). In addition, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). As long as the prior art teaches that it is

beneficial to treat cardiac hypertrophy and hypertension with a PKC inhibitor, it is not required that the artisan of ordinary skill have the same reasons or expectations as Applicant does. All that is required is that the artisan of ordinary skill have a reasonable expectation of success and the Dempsey patent has been deemed by the Office to supply this.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg